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Public health significance of invasive mosquitoes in Europe

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Abstract

There are currently five invasive *Aedes* mosquito species known to be established in Europe, namely *Aedes albopictus*, *Aedes aegypti*, *Aedes japonicus*, *Aedes atropalpus* and *Aedes koreicus*. *Aedes albopictus* and *Aedes aegypti* are the incriminated vectors in the recent outbreaks of chikungunya and dengue fever in Europe. However, both laboratory experiments and field observations indicate that these invasive mosquitoes have a potential to also transmit other pathogens of public health importance. Increasing travel and pathogen introduction, expansion of vector distribution, and both environmental and climatic changes are likely to raise the risk of pathogen transmission by these invasive *Aedes* mosquitoes. Their vector status and their involvement in pathogen transmission are dynamic processes that shape the future of mosquito-borne disease epidemiology in Europe. Beside vector surveillance, enhanced disease surveillance will enable the early detection of cases and the prompt implementation of control measures.

Keywords: *Aedes*, chikungunya, dengue, invasive, mosquito, vector species, vector-borne disease
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Invasive Mosquito Species in Europe

Invasive mosquito species are defined by their ability to colonise new territories and to cause or to be likely to cause harm to the economy, environment, or human health. Human actions are the primary means of introduction of invasive species. A considerable increase in the spread of invasive mosquitoes has been observed within Europe since the late 1990s, with the Asian tiger mosquito *Aedes albopictus* (Fig. 1) having continuously expanded its distribution, and several other container-breeding *Aedes* species now being reported from new countries every year (details about successive introductions and spread in Europe are given in [1]). To date, *Ae. albopictus* has colonised almost all Mediterranean countries, whereas the Asian bush mosquito *Aedes japonicus* (Fig. 2) is spreading widely in Central Europe. Two other species, *Aedes atropalpus* and *Aedes koreicus*, have been introduced on several occasions, leading to the establishment of populations at few foci. *Aedes triseriatus* was intercepted at a point of entry, and its establishment was prevented by the implementation of immediate control measures. Finally, the yellow fever mosquito *Aedes aegypti* (Fig. 3), which had been introduced into Europe during the 17–19th centuries, existed in southern Europe until its disappearance during the 20th century. This species has now returned, having recently established on Madeira as well as around the Black Sea coast (Russia, Abkhazia, Georgia). These invasive mosquito species are well adapted to synanthropic settings where they exploit the abundant sources of host blood, resting places and larval breeding sites (mainly man-made water containers) [2].

Mosquito-Borne Pathogens Transmitted by Invasive Mosquitoes in Europe

Although mosquito-borne diseases (MBDs) represent a lower burden in temperate compared to tropical regions where they pose a substantial impact on the countries' socio-economic

FIG. 1. *Aedes albopictus*, female. Source: F. Schaffner/Avia-GIS.

FIG. 2. *Aedes japonicus*, female. Source: F. Schaffner/Avia-GIS.

FIG. 3. *Aedes aegypti*, female. Source: F. Schaffner/Avia-GIS.

development, there have always been both endemic and epidemic autochthonous MBDs in Europe. Concern is now rising as both vectors and pathogens are increasingly being introduced by international travel and trade. Some of these diseases are emerging or are reappearing after a long period of absence. Their occurrence is often associated with changes in ecosystems, human behaviour, and climate [3].

The first notable outbreak of a MBD attributed to invasive mosquitoes in Europe occurred in 2007 in Ravenna, Italy, where more than 200 confirmed chikungunya cases were reported between July and September [4–7]. The index case was most likely a traveller returning from the state of Kerala, India, and the first local case was a relative that he visited [8]. Indeed, the strain that caused the outbreak in Italy was genetically similar to the strains from the Indian subcontinent and showed the mutation that is believed to be better adapted to *Ae. albopictus* [6]. The rapid spread of the infection from one index case demonstrated the efficiency of local *Ae. albopictus* populations to transmit chikungunya virus (CHIKV). The second autochthonous transmission of CHIKV in Europe occurred in southern France (Fréjus, department of Var) in 2010. The presumed index case who had returned from Rajasthan, India, sought medical care in late August and lived in the close vicinity of one of the two local cases who developed symptoms in September. The origin of the viral strain circulating in France was confirmed to be from northern India [9].

In the same year, two cases of autochthonous dengue fever occurred in Nice, France. This was the first local transmission of dengue virus (DENV) in Europe, since the major dengue epidemic of 1927–1928 in Greece where *Ae. aegypti* was implicated as the vector [10]. The first patient developed symptoms in late August 2010 and was detected through a routine enhanced surveillance system coordinated by the French authorities in the departments where *Ae. albopictus* had become established. The second case lived near the first case and developed symptoms by mid-September 2010 [11]. Subsequently, Croatia was the second country in Europe with autochthonous transmission of DENV in 2010 [12]. The first case was reported by the German health authorities that notified a laboratory-confirmed case in a German citizen returning from southern Croatia. The patient had spent 2 weeks on the Pelješac peninsula in early August [13]. A second case was reported in late October through active case finding in the same village where the infected tourist had stayed [12]. In addition, further evidence of indigenous transmission was suggested by positive laboratory results from 14 healthy individuals [12] and by a sero-prevalence survey using a random sample of the population living in the area [14]. Currently, a large outbreak of dengue fever is on-going in the Portuguese Autonomous Region of Madeira [15]. The epidemic started in October 2012 and by early January 2013 more than 2000 cases of dengue fever had been reported, with an additional 70 cases reported among European travellers returning from the island [16]. The presence of *Ae. aegypti* in Madeira has been known since 2005 but this is the first recorded outbreak of dengue on the island.

Since the 2007 outbreak of chikungunya in Italy, it is acknowledged that Europe is vulnerable for transmission of 'tropical' arboviruses, particularly in regions where *Ae. albopictus* or *Ae. aegypti* are present.

Potential Vector Role of Invasive Mosquitoes

Outside Europe, *Ae. albopictus* was implicated in transmission of CHIKV causing large scale disease outbreaks in the Indian Ocean and south Asia since 2005 [17]. Previously, *Ae. albopictus* was responsible for DENV transmission in the 1977–78 Reunion Island epidemic, in an outbreak in Hawaii in 2001–2002 [18] and again in Reunion Island (2004) [19], Gabon (2007) [20], and Mauritius (2009) [21]. *Aedes albopictus* is also a known vector of *Dirofilaria* filarial nematodes, which primarily are parasites of dogs but can also affect humans. Recent evidence of transmission by Italian *Ae. albopictus* populations [22,23] has been linked to an increase in prevalence of human dirofilariosis [24]. Other arboviruses important to human health that have been isolated from field-collected *Ae. albopictus* or for which laboratory transmission has been demonstrated [25] include Eastern equine encephalitis (EEEV) [26,27], Jamestown Canyon virus (JCV) [28], Japanese encephalitis virus (JEV) [25], La Crosse virus (LACV) [29,30], Venezuelan equine encephalitis virus (VEEV) [31,32], and West Nile virus (WNV) [33,34]. Field isolations and experimental infection studies alone, however, simply indicate the potential of a mosquito species to transmit these viruses but cannot prove its epidemiological role. Major dengue fever epidemics due to *Ae. aegypti* occur in the Americas, South East Asia and the western Pacific, and the disease is now endemic in >100 countries worldwide [35]. When this mosquito was widespread in southern Europe, it was responsible for large epidemics of dengue and yellow fever [10,36,37]. *Aedes aegypti* has recently been implicated in outbreaks of chikungunya, notably in Kenya and the Comoros Islands [38]. It is also a highly effective vector of yellow fever virus (YFV) in Africa and South America [39]. Historically, local outbreaks of yellow fever were reported from several ports in Europe (France, Great Britain, Italy, Portugal, Spain) in the 19th century following importations of the vector and viraemic passengers aboard vessels, with occasional large inland outbreaks where *Ae. aegypti* was established (e.g. Barcelona, Lisbon) [37]. Imported yellow fever cases are occasionally noted across Europe [40–42] with high case-fatality rates. In addition, *Ae. aegypti* was suggested as a vector of Zika virus (ZIKV) owing to virus isolation from field collections [43] and virus transmission under laboratory conditions [44].

Regarding the other invasive species, laboratory competency studies have shown the ability of *Ae. atropalpus* to transmit LACV [45], WNV [46] and other arboviruses causing encephalitis, but its importance as a vector of human pathogens is still not clear [47]. Field-collected *Ae. japonicus* have been found positive for WNV on a number of occasions in the US [48], and laboratory studies showed its high vector competence for WNV [46,49] and also for DENV [50], JEV [51], and LACV [52], whereas it was a moderately efficient vector for CHIKV [50], EEEV [53] and Saint Louis encephalitis virus (SLEV) [54]. However, its role in the transmission of these viruses under natural conditions remains unclear [55]. In North America, *Ae. triseriatus* is a known vector of LACV causing serious disease in humans [56,57], and JCV has repeatedly been isolated from field-collected specimens in the US [58]. It is also suggested to be a possible bridge vector for WNV, based on virus isolations from field collections [59] and vector competence demonstrated under laboratory conditions [60]. Other laboratory studies have shown vector competence for VEEV [61], EEEV, Western equine encephalitis virus (WEEV), DENV, SLEV and YFV [62]. *Aedes koreicus* has been linked to outbreaks of JEV [63] and *Dirofilaria* [64] but is not a confirmed vector of either pathogen.

Invasive Mosquitoes in Europe: A Growing Threat to Public Health?

Pathogen transmission by arthropod vectors depends on multiple factors which define their vectorial capacity *C*, i.e. the daily rate of future inoculations originating from a currently infective source. In the equation $C = b\ m\ a^2\ p^t/(-\ln p)$ [65], where b is the vector competence, i.e. the proportion of vectors that develop infective pathogen stages; m the vector density in relation to host density; a the vector's daily blood-feeding rate; p the vector's daily survival rate; *t* the duration of the pathogen's extrinsic incubation period in days. The vector capacity is specific to a species population in a defined natural context. The vector competence (b) refers to innate factors influencing the ability of a vector to transmit a pathogen. It is of primary importance, and it can be assessed in the laboratory by experimental infection, indicating the potential for involvement in transmission (Table 1), which is specific to each mosquito species and may vary between populations of a defined species [66,67]. DNA mutation of an arboviral protein can alter the transmission efficiency of a mosquito species, as observed in *Ae. albopictus* for CHIKV where a single amino acid substitution led to a reduction of the extrinsic incubation period and to an increase in transmission efficiency [68,69]. Besides being competent for a pathogen, a mosquito species needs to both sustain pathogen development under natural temperature ranges (*t*) and have a sufficient daily survival rate (p) to transmit the pathogen. Population density (m) and vector-host contact rate (a) need to be high enough to sustain the transmission cycle and, in cases where the pathogen has non-human reservoir hosts, the mosquitoes must blood-feed on both these animal hosts and humans.

TABLE 1. Main mosquito-borne pathogens that can be transmitted by invasive aedine mosquitoes

Pathogen	Genus	Clinical importance	Disease occurrence	Role of invasive species (confirmed[a]/ laboratory[b])
Chikungunya virus (CHIKV)	Alphavirus	Chikungunya infection can cause fever, myalgia, rash and strong arthralgia which often lasts for months in up to 65% of patients [88]; Clinical manifestations observed during an epidemic on La Reunion included severe hepatitis, severe maternal and foetal disease and meningoencephalitis [89]; There is currently no licensed vaccine against CHIKV [90]	Endemic in Africa and Asia; Frequently imported into Europe	***Ae. aegypti*** ***Ae. albopictus*** *Ae. japonicus*
Eastern equine encephalitis virus (EEEV)	Alphavirus	Severe cases of EEEV infection involving encephalitis begin with the sudden onset of headache, high fever, chills, and vomiting; The illness may then progress into disorientation, seizures, or coma, with fatality rates reaching up to 70% during some epidemics [91]	Americas; No evidence of introduction into Europe to date	*Ae. albopictus* *Ae. triseriatus*
Venezuelan equine encephalitis virus (VEEV)	Alphavirus	Largely subclinical, however can cause a nonspecific viral syndrome and rarely neurological complications such as encephalitis, more frequently in children than in adults, including death (fatality rate of 1 to 3%) [91,92]	Endemic in the Americas; No evidence of introduction into Europe to date	*Ae. albopictus* *Ae. triseriatus*
Western equine encephalitis virus (WEEV)	Alphavirus	Symptoms range from mild flu-like illness to severe encephalitis, coma and death, with a fatality rate up to 5%, and higher manifestation rates in children and in elderly persons [91]	Endemic in western part of North America; No evidence of introduction into Europe to date	*Ae. triseriatus*
Jamestown Canyon virus (JCV)	Bunyavirus	Probably most cases are subclinical, and rare human clinical cases show mild febrile illness and at some occasions acute central nervous system infection including meningitis and encephalitis [58,93]	Endemic in North America; No evidence of introduction into Europe to date	*Ae. albopictus* *Ae. triseriatus*
Dengue virus (DENV)	Flavivirus	Dengue consists of 4 viral serotypes; The infection causes a flu-like illness which includes fever, intense headache, muscular and joint pain, anorexia, nausea, vomiting and rashes; Sometimes it leads to life-threatening complications including severe bleeding and shock [21,94]; Severe dengue case fatality rates can reach 50% in untreated cases [78]; There is no vaccine available but several candidates are under clinical trials [95]	Endemic in Africa, Americas and Caribbean, Asia; Frequently imported into Europe	***Ae. aegypti*** ***Ae. albopictus*** *Ae. japonicus* *Ae. triseriatus*
Japanese encephalitis virus (JEV)	Flavivirus	Most cases are subclinical or result in mild symptoms only; However, a small percentage of cases develop encephalitis, with symptoms including sudden onset of headache, high fever, disorientation, coma, tremors and convulsions; It affects primarily children, fatality rate ranges from 10 to 35% and as many as 35% of survivors may have serious life-long neurologic sequelae [92]; Currently the most important mosquito-transmitted arbovirus causing encephalitis in the world, causing 30,000 to 50,000 human cases every year [91]; Vaccines are available	Endemic in Asia; No clear evidence of introduction into Europe to date	*Ae. albopictus* *Ae. japonicus* *Ae. koreicus*
St. Louis encephalitis virus (SLEV)	Flavivirus	Most cases are subclinical; Initial symptoms in clinically apparent cases (less than 1%) include fever, headache, nausea, vomiting, and tiredness; Severe neuroinvasive disease (often involving meningoencephalitis) occurs more commonly in older adults; In rare cases, long-term disability or death can result [96]	Endemic in the Americas; No evidence of introduction into Europe to date	*Ae. japonicus* *Ae. triseriatus*
West Nile virus (WNV)	Flavivirus	80% of WNV infection cases are subclinical, and 20% present mild influenza-like illness (fever, headache, body ache); Less than 1% of the cases develop more severe disease, such as encephalitis, meningitis or meningo-encephalitis, mainly in the elderly with fatality rates up to 20% [92]	Worldwide	*Ae. albopictus* *Ae. atropalpus* *Ae. japonicus* *Ae. triseriatus*
Yellow fever virus (YFV)	Flavivirus	YFV can cause systemic disease including fever, jaundice, haemorrhage and renal failure; Approximately 200,000 cases are reported annually [97]; Symptoms are present in about 1 in 7 of those infected [42] and the mortality rate is 20-50%; There is an effective live-attenuated virus vaccine for YFV which can help to prevent the disease [92]	Endemic in Africa and South America; Occasionally imported into Europe	***Ae. aegypti*** *Ae. triseriatus*
Zika virus (ZIKV)	Flavivirus	ZIKV can cause headache, rash, malaise and back pain [98]	Epidemic in Africa, Asia	*Ae. aegypti*
La Crosse virus (LACV)	Orthobunyavirus	LACV can cause serious neuroinvasive disease in humans (fatality rate of 0.3%); It is the common cause of paediatric arboviral encephalitis in the US with 40 to 170 cases reported annually and 90% of those infected are under the age of 15 [56]; Case numbers, however, are suspected to be underestimated [57]; Prior to WNV spread it was considered one of the most important mosquito-borne diseases in the US [45]; Most human infections occur from July to September [56]	Endemic in northern America; No evidence of introduction into Europe to date	*Ae. albopictus* *Ae. atropalpus* *Ae. japonicus* ***Ae. triseriatus***
Dirofilaria immitis, D. repens	*Dirofilaria*	In most human infections, larvae are destroyed by the immune system but in some cases, adult worms can develop, resulting in pulmonary or subcutaneous infections [99]	Endemic in southern Europe and the Americas	***Ae. albopictus*** *Ae. koreicus*

[a]'Confirmed' refers to evidence of the implication of a species (in bold characters) as vector for a defined pathogen on the field.
[b]'Laboratory' refers to demonstration of the ability of a species (in regular characters) to transmit a defined pathogen in laboratory experiments (vector competence).

Introduced mosquitoes may affect human health by (i) concurrently harbouring novel pathogens, (ii) transmitting native pathogens, or (iii) transmitting novel pathogens that were independently introduced [70]. The first scenario occurred during the 18th and 19th centuries in Europe with *Ae. aegypti* carrying YFV and DENV, causing disease outbreaks in ports and other places [10,71]. In the second scenario, the transmission rate of an indigenous pathogen may increase because of a high vector capacity of the invasive vector, as observed for *Dirofilaria* transmission in Italy in areas colonised by *Ae. albopictus* [24]. The third scenario appears to be the most common one for disease emergence, and it applies to the recently observed transmission of DENV and CHIKV, with various time periods elapsed between the introduction of the vector and the first outbreak (e.g. first CHIKV transmission occurred 17 years after the establishment of *Ae. albopictus* in Italy but only after 4 years in southern France), depending upon the global context (e.g. frequency and intensity of epidemics in dengue-endemic areas). The first and third scenarios have the potential to lead to large disease outbreaks, in particular because of a limited immunity of individuals in a population.

Considering the increasing frequency of both dengue and chikungunya epidemics worldwide and the movement of viraemic hosts, it is expected that new autochthonous cases of dengue and/or chikungunya fever will occur in the future [14]. It is estimated that 22.5 million travellers arrive in Europe each year, and as many as 185 000 of these could be viraemic for CHIKV [72]. Environmental changes such as land cover change or changes in weather patterns are known to impact vector-borne disease transmission [73]. Climate change could facilitate higher mosquito densities of *Ae. albopictus* or its establishment or spread beyond the current boundaries. It may result in transient summer expansions, or new foci of established populations, at locations where temperature and humidity are more suitable, thus enhancing the transmission potential for CHIKV and DENV in temperate regions [38,74–76]. However, demographic- and anthropogenic-driven environmental changes combined with globalisation and inefficient public health measures are considered the principal driving forces for the emergence and global spread of dengue in the past 40 years [77]. *Aedes albopictus* mosquitoes have the propensity to feed on multiple hosts and, therefore, contribute to the risk of transmission of zoonotic disease agents, whereas the strict anthropophily of *Ae. aegypti* favours transmission of anthroponosis [25]. Indeed, *Ae. albopictus* is considered to play a minor role compared to *Ae. aegypti* in DENV transmission, due to differences in host preferences and to lower vector competence [25,66]. In summary, the presence of *Ae. aegypti* and *Ae. albopictus* in Europe and the increasing number of overseas travellers may increase the risk of transmission of DENV and CHIKV in Europe [78]. *Aedes japonicus* deserves attention regarding its potential to transmit pathogens, including DENV and CHIKV, owing to high population densities in urban environments, its continuing spread in central Europe, its vector competence for several viruses under laboratory conditions, and its anthropophilic nature [F. Schaffner unpublished data, 50,79–81]. The other invasive species discussed here (*Ae. atropalpus*, *Ae. koreicus*, *Ae. triseriatus*) currently represent a very low risk for public health in Europe, considering their limited distribution. Given the recent developments, surveillance of all invasive aedine mosquitoes is now essential to detect early the presence of these mosquitoes, to assess the risk of MBDs and to prepare for the control of disease outbreaks [2]. The elimination of the species at an early stage of introduction, before it becomes widely established, has been achieved at some foci (e.g. in France [82], Italy [83], and The Netherlands [84,85]). When the species is widely established, the purpose of the control is usually limited to reducing the risk for disease transmission and biting nuisance. A number of control methods are commonly used such as source reduction, pesticide application, biological control, and public education. These methods are often combined as an integrated vector management strategy which so far seems to give the best results [86,87]. However, the control of *Ae. albopictus* has so far proven difficult with the currently available control methods and alternative innovative techniques are needed [1] as well as strategies to prevent the introduction of invasive *Aedes* species. Co-ordination among countries will be essential considering the cross-boundary aspects of the problem. Furthermore, fundamental knowledge on the relevant breeding places, host preferences and longevity of these invasive mosquito species under European conditions as well as on their vector competences for important viruses is required to better target and control these species. Vector status is a dynamic process that in the future could impact significantly on MBD epidemiology. Beside vector surveillance, enhanced disease surveillance will enable the early detection of cases and the prompt implementation of control measures.

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Transparency Declaration

The authors declare no conflicts of interest.

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